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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/539,534

02/13/2006

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EXAMINER

SULLIVAN, DANIEL M

ART UNIT

PAPER NUMBER

1636

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.		Applicant(s)	
	10/539,534		UMEDA ET AL.	
	Examiner		Art Unit	
	Daniel M. Sullivan		1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 March 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 7-14, 23 and 24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 7-14, 23 and 24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 17 June 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/13/06</u> . | 6) <input checked="" type="checkbox"/> Other: <u>See Continuation Sheet</u> . |

Continuation of Attachment(s) 6). Other: Entrez Gene search results for ZO-1.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 12 February 2006 as the US National stage of international application PCT/JP03/16549 filed 24 December 2003, which claims benefit of Japanese patent applications JP 2002-371621 filed 24 December 2002 and 2003-76877 filed 20 March 2003. The preliminary amendments filed 17 June 2005, 13 February 2006 and 27 March 2008 have been entered. Claims 1-22 were originally filed. Claims 7-9, 11, 12, 14, 18, 19 and 22 were amended and claims 23 and 24 were added in the 13 February preliminary amendment. Claims 1-4, 7-14, 23 and 24 are currently pending.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-4, 7-14, 23 and 24) in the reply filed on 27 March 2008 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-14, 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116).

The claims of the instant application are directed to a gene targeting vector comprising an entire or partial region of the ZO-1 gene. As the application does not include a definition of “the ZO-1 gene” and contemplates targeting the ZO-1 gene of a wide range of non-human animal species (see, e.g., page 9, lines 29-32, which names mice, dogs, rats, hamsters, rabbits, pigs, bovines, horses, chickens, monkeys, sheep, goats, and cats as merely examples), the claims construed as broadly as reasonable in light of the specification cover a vector comprising a ZO-1 gene from any species of animal that is not a human.

The Guidelines for Written Description state: “when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus” (Federal Register, Vol. 66, No. 4, Column 3, page 1106). “The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus” (MPEP §2163(3)(a)(ii)).

In the instant case, the application discloses a single species within the genus “ZO-1 gene” (i.e., the mouse ZO-1 gene set forth in the instant application as SEQ ID NO: 1). In addition to the disclosure of this single species, the application provides the generic assertion, “Nucleotide sequences of the ZO-1 gene are already known, and information related to ZO-1 gene nucleotide sequences can be easily obtained from a public gene bank known to those skilled in the art.” However, a review of the art indicates that dog, rat, zebrafish (*Danio rerio*), *D. melanogaster* and *C. elegans* are the only species other than mouse for which the nucleotide sequence of ZO-1 genes are known. (See, e.g., the attached Entrez Gene search results for ZO-1.)

The single species disclosed in the application and the five additional species known in the art do not demonstrate possession of a ZO-1 gene from the broad scope of any species of animal (many thousands of genes) because the nature of species homologs is that they are each structurally distinct and the identity of their structural variation cannot be predicted based on the structure of any other species homolog. See *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206, 18 USPQ2d 1016 at 1021 (“We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated.”) (citations omitted). In such instances the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor’s idea of the invention. *Burroughs Wellcome Co. v. Barr Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir.

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1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention.

Although the teachings of the specification might enable one of skill in the art to isolate ZO-1 genes from other species of animal, an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property (i.e., it is a ZO-1 gene) because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all DNA's that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8-12, 14 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Itoh et al. (1993) *J. Cell Biol.* 121:491-502 (made of record in the IDS filed 13 February 2006) as evidenced by Fermentas Life Sciences (2006) "pBluescript II KS(+/-), pBluescript II SK(+/-): description & restriction map" downloaded from <http://www.fermentas.com/techinfo/nucleicacids/mappbluescriptiiskks.htm>, 12 May 2008.

The claims are directed to a gene targeting vector for introducing an exogenous gene into the ZO-1 gene region in a non-human animal, wherein the vector comprises the exogenous gene and an entire or partial region of the ZO-1 gene. The application provides no limiting definition of a targeting vector. In addition, any vector comprising nucleic acid sequence of a ZO-1 gene would be capable of homologous recombination with the endogenous gene such that any gene comprised in the vector in addition to the ZO-1 gene would be introduced into the ZO-1 gene region. In view of this, independent claim 1 is construed as encompassing any vector comprising sufficient ZO-1 gene sequence that it would be capable of homologous recombination with a ZO-1 gene in an animal and further comprising an additional gene.

Itoh et al. teaches cloning of the mouse ZO-1 cDNA and that each of the clones obtained was subcloned into a pBluescript SK(-) vector. (See especially the section entitled "cDNA

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Library Screening and DNA Sequencing" on page 492.) The map of pBluescript II shows that the vector comprises at least two heterologous genes (i.e., lacZ and bla(Ap^R). Thus, the vectors of Itoh et al. comprise an exogenous gene and a partial region of the ZO-1 gene, wherein the vector could be used to introduce an exogenous gene into the ZO-1 gene region in a mouse. Therefore, the vector anticipates the targeting vector of the instant claim 1.

In addition, the vector of Itoh et al. comprises a partial region of the ZO-1 gene placed upstream and downstream of the exogenous gene according to dependent claim 2. (Note that because the vector is circular each gene within the vector is both upstream and downstream of every other gene in the vector.) The vectors of Itoh et al. comprise the entire ZO-1 cDNA sequence and, therefore, comprise exon II according to claim 3. The bla(Ap^R) and lacZ genes each comprise a promoter capable of transcribing the exogenous gene according to claim 8 and either of the bla(Ap^R) or lacZ genes might be considered a marker gene expression cassette according to claim 9.

Claim 10 recites, "...an exogenous gene is placed adjacent to the downstream of a marker gene expression cassette." It is noted for the record that the downstream of a cassette in a linear DNA extends from the end of the marker gene expression cassette to the end of the DNA. Therefore, the only position "adjacent to the downstream" of the cassette is within the cassette itself or upstream of the cassette. As in the instant case the vectors are circular and, as discussed above, all genes can be viewed as upstream of all other genes, the limitations of claim 10 are met by the bla(Ap^R) and lacZ genes of the pBluescript vector.

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The bla(Ap^R) and lacZ genes are marker gene expression cassettes according to claim 11, the bla(Ap^R) gene is a drug resistance gene according to claims 12 and 23, and the gene is a mouse gene according to claim 14.

Itoh et al. teaches a vector comprising all of the elements of the vector presently claimed. Therefore, the claims are anticipated by Itoh et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (1991) *Devel.* 113:295-304 in view of LeMoullic et al. (1990) *Proc. Natl. Acad. Sci.* 87:4712-4716 and Itoh et al. (*supra*).

The claims are directed to a gene targeting vector for introducing an exogenous gene into the ZO-1 gene region in a non-human animal, wherein the vector comprises the exogenous gene and an entire or partial region of the ZO-1 gene and wherein the vector is used for generating a non-human animal or non-human animal cell expressing an exogenous gene.

Fleming et al. teaches a method of investigating ZO-1 expression in embryos using an antibody against the ZO-1 protein.) See especially the abstract and results section.

LeMoullic *et al.* teaches a method of following the tissue specific expression of a gene by inserting a marker gene into a targeting vector and integrating the targeting vector into an endogenous gene such that the endogenous gene is inactivated and the marker gene is placed under the control of the endogenous promoter (see especially the section entitled “*lacZ* Expression in Chimeric Embryos” in the right column on page 4715).

As described above, Itoh et al. teaches the sequence of the mouse ZO-1 gene.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a targeting vector that could be used for generating a non-human animal expressing an exogenous gene in order to make a mouse comprising a marker gene inserted into a target gene that could be used to study the expression of the gene as taught by LeMoullic *et al.* in order to study cell specific and developmental expression of the ZO-1 gene, which is the nature of the problem to be solved in the northern blot methods of Fleming et al. In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized “the need for caution in granting a patent based on a combination of elements found in the prior art,” (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on it

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precedent that “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” (*Id.* At 1395.)

In the instant case, it was known in the art that immunochemistry and expression of a reporter gene from a construct integrated into a mouse gene using a targeting vector were alternative means to assay gene expression. One could have substituted the reporter gene assay described by LeMoullic et al. for the immunochemistry method described by Fleming et al. with the predictable outcome of an effective method of assaying for cell specific gene expression. As it would be obvious to practice the method of LeMoullic et al. using a vector targeted to the ZO-1 gene, the vector of the instant claims, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

Claims 1-3, 7-12, 14 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (1994) *Scientific American* 270:34-41 in view of Itoh et al. (*supra*).

The limitations of independent claim 1 are described herein above.

Capecchi teaches transforming a cell with a nucleic acid construct comprising a disruption in the HoxA-3 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous HoxA-3 locus, and using said cell to generate a mouse whose genome comprises a disruption in the HoxA-3 gene. Capecchi further teaches that such disruptions are produced using targeting vectors comprising first and second polynucleotide sequences homologous to the target gene and a selectable marker (see especially the drawing at the top of page 36 and the caption thereto). Capecchi differs from the claimed invention in that the

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targeting construct does not disrupt the ZO-1 gene. However, at the time the claimed invention was made, Itoh et al. had disclosed the cloning of the mouse ZO-1 gene.

It would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to make a targeting vector for a disruption in a targeted gene as taught by Capecchi wherein the gene was the ZO-1 gene as taught by Itoh et al. One of ordinary skill in the art would have been sufficiently motivated to replace the Hox3A gene with the ZO-1 gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse. See, e.g., teachings of Capecchi such as, “Gene targeting offers investigators a new way to do mammalian genetics—that is, to determine how genes mediate various biological processes. This technique was needed because the classical methods of genetics, which have been highly successful in analyzing biological processes in simpler organisms were not readily adaptable to organisms as complex as mammals” (first full paragraph on page 35). In view of this, one of ordinary skill in the art would have been sufficiently motivated to produce a targeting vector comprising sufficient sequence from a mouse ZO-1 gene to target the vector into the mouse ZO-1 gene and an exogenous selectable marker in order to disrupt the gene in a mouse characterizing the roles of ZO-1 in mammalian biological processes.

Thus, the invention of independent claim 1, as a whole, would have been obvious to one of ordinary skill in the art at the time was made. In addition, the limitations of the dependent claims are also found in the art. Specifically, Capecchi teaches construction of a targeting vector wherein a neomycin resistance gene is inserted within an exon of the targeted gene and thymidine kinase resistance gene is inserted downstream of the neomycin resistance gene. (See the drawing on page 36 and the caption thereto.) This teaching, in view of the disclosure of a

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nucleic acid comprising the entire coding sequence from the mouse ZO-1 gene renders obvious the targeting vector of claims 2, 3, 7-12 and 23.

For these reasons, the claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC §103(a) as obvious over the art.

Claims 13 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (*supra*) in view of Itoh et al. (*supra*), as applied to claims 12 and 23 herein above, and further in view of Blake et al. (1997) *BioTechniques* 23:690-695.

Claims 13 and 24 are directed to the method of claims 12 and 23, respectively, wherein the drug resistance gene expression cassette is a DNA fragment comprising β -geo. As described above, the invention of claims 12 and 23, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the teachings of Capecchi and Itoh et al. However, Capecchi teaches constructing targeting vectors comprising a neomycin resistance gene rather than a β -geo resistance gene.

Blake et al. teaches a marker gene comprising a fusion of the beta-galactosidase and neomycin resistance marker genes (i.e., β -geo; see especially Figure 1 and the caption thereto) and teaches that the marker gene is useful for identifying cells expressing transgenic or gene targeted constructs *in vivo*. (See especially the final sentence of the Abstract and page 695, lines 21-25.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the β -geo marker gene of Blake et al. for the neomycin resistance gene in

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the targeting vector of Capecchi in view of Itoh et al. In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized “the need for caution in granting a patent based on a combination of elements found in the prior art,” (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” (*Id.* At 1395.)

In the instant case, the targeting vector of Capecchi in view of Itoh et al. differs from the presently claimed invention only in the substitution of a neomycin resistance marker gene for the β -geo marker gene recited in the claims. However, the β -geo marker gene and its use as a marker in gene targeting constructs was known in the art at the time the instant invention was made. Therefore, one could have substituted the β -geo marker for the neomycin resistance gene used in the targeting vector of Capecchi in view of Itoh et al. with the predictable outcome being a targeting vector useful in the construction of mice comprising targeted disruptions in the ZO-1 gene.

As the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of invention, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel M Sullivan/
Primary Examiner, Art Unit 1636